Orthotopic Transplantation During Early Infancy as Therapy for Incurable Congenital Heart Disease

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Since November 1985, 14 neonates and young infants have undergone orthotopic heart transplantation at Loma Linda University Medical Center (LLUMC) as therapy for hypoplastic aortic tract complex. Eleven (78%) survived surgery and are living and well today. Three perioperative deaths resulted: one due to perforated peptic ulcer, one due to necrotizing pneumonitis, and one due to graft failure unrelated to rejection. No late deaths occurred in the 1–29 months of follow-up, during which time noninvasive surveillance techniques were used. Immunosuppression was accomplished using cyclosporine and azathioprine. Steroids and antithymocyte globulin were used for identified rejection episodes only. Ordinary childhood infections were tolerated well. All survivors were normotensive. There was no late renal dysfunction. Although inadequate donor resources remain a significant limiting factor for transplantation therapy during early life, these results suggest that cardiac transplantation is effective therapy for selected neonates and young infants with incurable congenital heart disease.

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ORTHOTOPIC CARDIAC transplantation during early infancy offers an attractive surgical option for treatment of incurable congenital heart disease. As therapy for primary structural heart disease, transplantation is a concept overdue in application. It offers the promise of normal cardiovascular anatomy and physiology, as opposed to palliative interventions, and is now feasible during the earliest days and weeks of life. An estimated 10% of congenital heart disease is sufficiently complex as to be incorrectable by conventional surgery.[1] That translates to somewhat over 3000 North American babies annually who might benefit from heart or heart/lung replacement. Hypoplastic left heart syndrome (HLHS) represents just such a complex group of malformations. With rare exceptions, HLHS is lethal within the first few weeks of life. These infants, therefore, are a logical starting point for application of cardiac transplantation.

Reported here are a series of very young infants whose HLHS was managed at Loma Linda University Medical Center (LLUMC) by orthotopic cardiac transplantation. Patient selection and operative, perioperative, and follow-up management are all detailed. In addition, the advantages and limitations of this therapeutic modality are presented.

Methods

Since November 1985, 27 neonates and young infants (3.5 months and younger) with variations of HLHS have been accepted into the Loma Linda University Infant Heart Transplant Program as potential recipients. Fourteen (52%) of these infants had orthotopic cardiac transplantation. Each infant accepted for transplantation was managed according to a specific protocol formulated by the Loma Linda University Infant Heart Transplant Group. This protocol is based broadly on laboratory animal investigations and on a previously devised protocol used in the management of a premature newborn infant with HLHS, who was treated by cardiac xenotransplantation.[2,3]

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TABLE 1. *Recipient Inclusion Criteria*

1. Gestational age greater than 36 weeks* and birth weight greater than 2200 g*
2. Age of less than 1 month*
3. Cardiac evaluation
   The diagnosis of hypoplastic left heart syndrome made by attending pediatrician or pediatric cardiologist.
   Echocardiographic confirmation of diagnosis.
4. Stable metabolic and hemodynamic status while receiving PGE-1 and other supportive measures (*e.g.*, cardiac inotrope, mechanical ventilation, parenteral nutrition)
5. Psychosocial evaluation
   The candidate should live within 60 minutes of LLUMC for a minimum of 9–12 months after transplant.
   Supportive family structure.
   The candidate's family should be capable of long-term intensive care of the child and be able to support the exceptional needs of the child.
6. No clinical suspicion of major sepsis.
7. Normal neurological evaluation.
8. Normal renal evaluation:
   If BUN > 30 and creatinine < 1.5, pediatric nephrology consultation to exclude gross renal abnormalities
   Abdominal ultrasonography study showing no significant renal malformations
9. Phenotypically normal.

* Relative criteria

Patient Selection Criteria

Inclusion criteria for acceptance as a potential infant transplant recipient are outlined in Table 1. This report considers only those infants with variants of the HLHS. At our institution, patients are excluded from consideration for transplantation on the basis of adverse medical factors, such as neurological compromise, end-organ failure, active infection (congenital or acquired), or significant dysmorphism. Consideration is also given to environmental factors that might adversely affect medical compliance. For example, families are required to relocate temporarily in order to be readily available during the first post-transplant year, when surveillance is most intense.

Infant heart donors must meet brain death criteria in compliance with the Uniform Determination of Death Act[4] and guidelines for the determination of brain death in children as endorsed by an Ad Hoc Task Force Committee (comprised of representatives from the American Academy of Neurology, American Academy of Pediatrics, American Bar Association, American Neurological Association, Child Neurology Society, and National Institutes of Neurological Communicative Diseases and Stroke[5]). In addition, donors must share compatible ABO blood grouping and be similar in size to their respective recipients, be free of infection, and have normal cardiac anatomy with stable hemodynamics. Most infant donors will have had varying periods of cardiopulmonary resuscitation, yet many are suitable for multiorgan donation. Availability of newborn and young infant donors is gradually evolving as a function of professional and public awareness and commitment.

Preoperative Management

A clinically suspected diagnosis of HLHS is confirmed by two-dimensional echocardiography. Cardiac catheterization is seldom required. Infants (particularly newborn) with confirmed HLHS are given a continuous intravenous (I.V.) infusion of prostaglandin E-1 (PGE-1) to ensure patency of the ductus arteriosus, and hence maintained systemic perfusion. Spontaneous or mechanical ventilation is accomplished in room-air, in an effort to balance pulmonary and systemic vascular resistances. This helps promote adequate systemic perfusion. Enteral or parenteral nutrition is commenced. Many newborns with HLHS are not suspected of having heart disease until spontaneous closure of the ductus arteriosus occurs. Frequently, they are first evaluated when severely compromised or moribund. Immediate correction of acidosis and/or hypoglycemia, infusion of PGE-1, room-air mechanical ventilation, and inotropic support are usually effective in saving these babies. Not infrequently, mechanical ventilation and inotropic support are discontinued in 24–48 hours, and the infant is maintained as described above.

At their familys' request (after appropriate counseling), infants with HLHS are typed for ABO antigens and registered with the United Network for Organ Sharing (UNOS) through the regional organ procurement agency. After donors are confirmed and organ procurement arrangements are in progress, the potential recipients are given a continuous I.V. infusion of cyclosporine (CSA) of 0.2–0.4 mg per hour. Enteral feedings are discontinued at this time. Generally, donor infants are transported intact to LLUMC whenever possible. In this series, 12 of 14 (86%) donor families complied with this request. By implementing this policy, cold ischemic time of the donor heart was minimized, and multiorgan procurement was greatly simplified.

Operative Management

The donor. Hearts procured at any considerable distance from LLUMC are obtained by inflow occlusion and the use of cold crystalloid cardioplegia. They are then stored and transported in a cold saline bath. On-site procurement of the heart alone is accomplished in a similar manner. For multiorgan retrieval, donor infants receive extracorporeal circulation and are cooled to profound levels of hypothermia with asanguinous perfusate. The brachiocephalic artery is used for arterial cannulation, and the right atrial appendage is used for venous cannulation. During a brief period of circulation

arrest, the ductus arteriosus is ligated against the aorta, and the heart, aortic arch, and proximal descending aorta are removed. The pleural spaces are opened widely, and heart/lung machine suckers are placed in each pleural space. The arterial cannula is transposed to the open descending aorta and secured. Hypothermic perfusion is then recommenced, and liver/kidney removal accomplished.

The heart is trimmed for implantation as previously described,[6] with one exception. Rather than bevelling the distal donor aorta, the aorta is cut off squarely and incised for a length of about 20 mm along the greater curvature. This provides a greater distal aortic diameter opposite the recipient coarctation site, and thus possibly reduces the risk of late recoarctation. (M. Kanakriyeh, MD, et al, unpublished data, 1988)

The recipient. On-site donor and recipient infants are transported to the operating room simultaneously. Central vascular lines are inserted as required, with emphasis on asceptic technique. The left groin has been used most frequently for insertion of central arterial and venous lines. Not infrequently, the recipient's central vascular lines are already in place for administration of PGE-1 and CSA. The recipient and donor are then prepared and draped. The donor heart is removed, and orthotopic cardiac transplantation is accomplished as previously described.[6] Implantation required extended aortic arch reconstruction in each of the 14 transplants performed for treatment of HLHS variants at LLUMC. On occasion, however, aortic arch reconstruction is not required, thus simplifying the procedure.[7] In this series of transplants, all anastomoses were completed during circulatory arrest. In general, however, should time become a critical factor, the pulmonary arterial anastomosis may be accomplished during rewarming perfusion.

Perioperative Management

Many of the infant recipients in this series entered the operating room with the aid of assisted ventilation and inotropic support. After transplantation, all required 2 days or more of intubation and ventilator assistance. Each infant benefited from some form of inotropic support (usually isoproteronal and/or dopamine) in a low-maintenance dose. Additional pulmonary vasodilatory medication was not needed. Three newborns required perioperative peritoneal dialysis. In each case, anuria commenced before transplantation as a result of compromised distal aortic perfusion pressure, and resolved within 2–3 days after surgery. Perioperative seizures did not occur in this series of infants, despite their catastrophic illness. Each patient made a satisfactory perioperative neurological recovery.

Table 2 summarizes the postoperative immunomanipulative therapy used with this series of recipients. On the day of surgery, a continuous I.V. infusion of CSA (0.2–0.4 mg per hour), was resumed. Target radioimmunoassay (RIA) whole blood levels of CSA ranged from 600–1000 ng/dl. CSA-induced perioperative acute renal failure was not observed. Oral CSA administration accompanied the onset of oral feedings (usually 3–5 days after surgery). I.V. CSA was discontinued 12 hours before administration of the first oral dose. The oral dose began at 4–8 mg/Kg/day, divided into two doses (one at 8:00 a.m. and one at 8:00 p.m.) Whole blood RIA trough levels of CSA were obtained daily at 7:00 a.m., and dosage was adjusted to attain CSA levels of 600–800 ng/dl.

TABLE 2. *Infant Heart Transplantation for Hypoplastic Left Heart Syndrome: Recipient Immunomanipulation Protocol*

Immunosuppression
Cyclosporine
First year whole blood levels: 400–600 ng/dl
After first year: 200–400 ng/dl
Azathioprine
First year: 3 mg/kg tapered to 0
Not administered after first year
Rejection protocol
Patient Condition
No symptoms (outpatient)
Mild symptoms (inpatient)
Moderate/severe symptoms (inpatient)
Medications
Prednisone
IV methylprednisolone + Prednisone
ATG + methylprednisolone + Prednisone
Immunoenhancement
Gammaglobulin
200–400 mg/Kg/dose
At least 3 doses before surgery
Multiple doses during administration of "Rejection Protocol"
Routine serial doses as needed for specific treatment of cytomegalovirus infection.

Four I.V. doses of methylprednisolone (25 mg/Kg) were given at 12-hour intervals immediately after surgery. Steroids were thereafter withheld unless a clinical diagnosis of graft rejection is made. Azathioprine (3 mg/Kg/day) was first administered 48 hours after transplantation, initially intravenously, and then orally, once per day. Azathioprine dosage was tapered to maintain a white blood cell count greater than 3500 per cubic millimeter.

The infants were immunoenhanced through administration of 300–400 mg/Kg of gamma globulin within the first 72 postoperative hours. Gamma globulin administration was repeated two to three more times during the initial postoperative hospitalization. A broad-spectrum antibiotic was given intravenously for 5–7 days.

Vascular lines were handled with strict aseptic technique and then removed when no longer essential. A single central venous catheter was kept in place for blood sampling purposes during the first 10–14 postoperative days.

Noninvasive postoperative transplant surveillance techniques were employed to monitor the infants for evidence of graft rejection and/or systemic infection.[8] Infants were examined carefully on a daily basis for evidence of fever, irritability, poor feeding, unexplained increase in resting heart rate, arrhythmia, excessive weight gain, hepatomegaly, or the presence of a gallop rhythm. Surveillance monitoring was undertaken each Monday and Thursday, commencing the second post-transplant week. Routine examinations included chest roentgenogram, electrocardiogram, and M-mode echocardiogram. Blood samples were obtained for performance of miniaturized assays, which include white blood cell count and differential, spontaneous blastogenesis, CSA level, blood urea nitrogen, creatinine, and creatine phosphokinsae isoenzyme level.

To date, laboratory and clinical experience suggest that none of these surveillance tools are entirely reliable for the diagnosis of rejection. However, a combination of changing factors, coupled with clinical intuition, has served to support a diagnosis of graft rejection with reasonable confidence. Reversal of abnormal findings after initiation of additional antirejection therapy (steroid and/or antithymocyte globulin) serves to substantiate the diagnosis of rejection.

After hospital discharge, the infants were followed in accordance with the protocol pertaining to outpatients, initially twice per week. In general, outpatient surveillance is more frequent during periods of suspected graft rejection or systemic infection, with outpatient visits becoming less frequent as the rejection-free interval lengthens. Beyond 6 months, recipients underwent outpatient evaluation only once per month. During the second post-transplant year, outpatient evaluations continued to be accomplished on a monthly basis; however, recipients and their families were permitted to reside and be examined at their point of origin. Full invasive diagnostic studies, including myocardial biopsy, were accomplished at the end of the first post-transplant year. Five of the oldest survivors were studied in this way. The generally excellent results of these studies have been reported previously. (M. Kanakriyeh, MD, et al, unpublished data, 1988)

Immunizations were begun between the third and sixth post-transplant month as described earlier.[9] Antibody response to routine immunization was adequate, although live-attenuated viral vaccines were not employed. Two of the recipients were exposed to chicken pox, one of whom developed self-limiting clinical manifestations of the disease.

Results

Eleven (78%) neonates and very young infants survived orthotopic cardiac allotransplantation as therapy for HLHS (Table 3). The last seven consecutive patients survived surgery and, like earlier survivors, are presently being followed as outpatients. Six of the last eight (75%) patients with HLHS registered for a donor heart underwent transplantation. This more recent experience implies better public and professional awareness of the need for infant donor organs. An average of 14.5 days were required to locate an appropriate organ donor for this series of transplants. Recipient age at operation varied between 3 hours and 3.5 months. Three of the infants were over 30 days of age at operation. Hypothermic circulatory arrest, ranging between 47 and 65 minutes (mean of 56 minutes), has been used in this series of transplants. Average hospitalization time following transplantation has been 27.5 days. All but one of the infants in this series were successfully treated for one or more early (first 6 post-transplant months) acute rejection episodes. One infant has not yet mounted an identifiable immune response to his graft. Minor childhood infections have responded well to specific antibiotic therapy. One recipient developed cytomegalovirus infection, which has been controlled by intermittent infusions of hyperimmune globulin. She is now clinically well.

Azathioprine was tapered during the second 6 post-transplant months and discontinued at 12 months. CSA dosage was adjusted to maintain whole blood RIA values at 200–400 ng/dl beyond the first year, when CSA became their sole immunosuppressive agent. None of the recipients experienced systemic hypertension, renal dysfunction, or late drug-related hirsutism. Growth and neurodevelopment have been generally within the normal range. Survival has now extended from 1 to 29 months, averaging 12.6 months. A unique and gratifying feature of this initial series of infant heart transplant recipients is the fact that there have been no late deaths. Three perioperative deaths (four to 13 post-transplant days) resulted from perforated peptic ulcer, nonrejection graft failure, and necrotizing pneumonitis. In the latter case, the infant was transplanted in the face of "treated" lobar pneumonia.

Discussion

Incurable congenital heart disease, such as HLHS, may be managed in several ways. Parents of these infants still have the option to accept, without therapy, the abbreviated natural history of the disease process. Such untreated infants invariably die, usually within the first 30 days of life. Although occasionally justifiable, this option is becoming less appropriate as potentially durable surgical modalities evolve. Parents may opt for multiple palliative reconstructive procedures, as originally described by Norwood et al,[10] in the hope of achieving prolonged survival and acceptable life quality. Overall attrition using multiple or "staged" palliative operations

TABLE 3. *Infant Heart Transplantation for Hypoplastic Left Heart Syndrome*

	Recipient			Donor			Wait for Organ Donor (days)	Date of Transplant	Assisted Ventilation (days)	Perioperative complications	Hospitalization (days)	Present Status						
Pt. #	Age (days)	Weight (kg)	Blood Type	Age (days)	Weight (kg)	Blood Type						Age (mo)	Weight (kg)	Immunosuppression	Clinical status	Renal function	Resting Blood Pressure	Comments
1	4	2.9	O+	8	4.0	O+	1	11-20-85	2	+ (see comment)	43	29	11.4	CSA	WH	N	N	Required perioperative peritoneal dialysis Mild neurodevelopmental delay Myocardial biopsy (—)
2	17	3.7	O+	15	3.8	O−	13	1-23-86	4	0	21	26	12.1	CSA	WH	N	N	30 mmHg gradient at distal arch without proximal hypertension Unresponsive to balloon aortoplasty Myocardial biopsy (—)
3	101	3.3	B+	9	4.5	O+	67	4-28-86	3	0	23	24	15.3	CSA	WH	N	N	Multiple rejections 1st 6 months 1 mild late rejection at 20 months Intermittently sheds CMV in urine Myocardial biopsy (—)
4	16	4.6	O+	12	4.0	O−	5	6-10-86	3	0	28	23	12.8	CSA	WH	N	N	Residual coarctation at distal arch Balloon Aortoplasty Gradient abolished Myocardial biopsy (—)
5	79	3.1	A+	2	2.5	O+	1	2-7-87	3	0	20	14	7.5	CSA	WH	N	N	Multiple rejections 1st 6 months Residual coarctation at distal arch Balloon aortoplasty Persistent 10 mgHg gradient Myocardial biopsy (—)
6	1	2.9	AB+	2	2.7	O+	6	10-16-87	7	+ (see comment)	35	6	6.8	CSA AZA	WH	N	N	Required perioperative peritoneal dialysis
7	11	3.6	B+	11	4.1	O+	3	10-26-87	1	0	36	6	6.4	CSA AZA	WH	N	N	—
8	86	4.0	O+	120	6.4	O+	22	11-20-87	5	0	21	5	6.3	CSA AZA Steroid (intermittent)	WH Recurrent rej. ther.	N	N	Multiple rejections 1st 6 months
9	18	2.5	A+	14	3.4	O+	16	1-30-88	6	0	26	3	5.2	CSA AZA	WH	N	N	—
10	8	3.7	O+	4	3.2	O+	5	2-14-88	2	0	17	2	5.0	CSA AZA	WH	N	N	No rejection episode
11	21	3.0	O−	21	3.3	O+	20	4-7-88	2	0	15	0.5	3.3	CSA AZA	WH	N	N	—
Average	33	3.4	—	20	3.8	—	14.5	—	3.5	—	27.5	12.6	—	—	—	—	—	—

Specific data regarding 11 survivors of orthotopic heart transplantation for hypoplastic left heart syndrome.
AZA = Azathioprine
N = normal
WH = well at home
CMV = Cytomegalovirus

remains steep, however, even in the most experienced hands. Life quality and the emotional and fiscal expenses of multiple high-risk operations are speculative issues relating to palliative management that have yet to be resolved.

Based on the limited experience presented here, parents may be offered yet another option: heart replacement by orthotopic cardiac transplantation. This approach, beginning with the day of surgery, results in virtually normal anatomy and physiology. In general, the perioperative period for these transplanted neonates has been pleasant and predictable. An average 3.6 days of assisted ventilation and a mean 27.5 days of hospitalization among post-transplant survivors support this notion. There have been no early or late reoperations to date, although three late survivors had balloon aortoplasty for distal aortic anastomotic gradients ranging from 24–30 mmHg. Three of the newborns in this series, all of whom had had acute renal failure before surgery, required postoperative peritoneal dialysis. Two of these infants survived surgery and regained adequate renal function within 36–48 hours. Their renal function is normal today.

Families have coped admirably with the transplantation experience. Many have relocated temporarily to accommodate postoperative surveillance. Families and extended families are given instruction about medicating and observing the transplanted infants. Frequent outpatient visits and occasional in-hospital observation are usually all that interrupt the normal flow of life for most of these families. As experience has broadened, the process has become less spectacular and more routine for all concerned.

The twin haunts of rejection and infection appear to be greatly reduced when transplantation is accomplished early in life (0–30 days). In fact, the newborn and/or slightly preterm newborn may be the best possible recipient of organ transplantation. As observed in the laboratory animal model,[11–13] host immune response is less aggressive and more easily controlled when transplantation is accomplished shortly after birth. Immunosuppression along with its side effects, (*e.g.,* serious infection, hypertension, and hepatorenal dysfunction) are minimized in this age group. The same cannot be said for infants transplanted after the first 30 days of life. Three of the recipients presented here were transplanted at 79, 86, and 101 days of age. Acute rejection was diagnosed and treated four to six times during their first 6 post-transplant months. These were the only recipients in whom overt clinical cardiac decompensation was observed at least once during a rejection episode, and they were the only recipients requiring antithymocyte globulin as rescue therapy to reverse the rejection response. Nevertheless, two of these three infants had routine late endomyocardial biopsies that were free of rejection and/or fibrosis. Experience suggests that the "immunologic privilege" documented among newborn recipients does not extend much beyond the first month of life.

A strong point can be made in support of *in utero* diagnosis of HLHS and other complex incurable cardiac malformations. A donor organ search begun at the 35th week of gestation would be likely to be successful. With a donor on-hand, the fetus may be delivered, begun on PGE-1, and transplanted almost immediately. This might be considered an ideal management plan for complex, incurable congenital heart disease. However, this sequence of events was experienced only once in this series of successfully transplanted recipients. (J. Johnston, RN, et al, unpublished data, 1988).

Noninvasive diagnosis of graft rejection appears to be reliable in this age group (0–30 days) of transplant recipients. Clinical cardiac findings, which are considered late manifestations of graft rejection in older children and adults, are very reliable and useful indicators in infants transplanted as newborns. Other clinical findings such as irritability, fever, and anorexia are supportive but nonspecific for graft rejection. The same may be said of the myriad of laboratory assays aimed at early identification of T-lymphocyte activation. The spontaneous blastogenesis assay may be a supportive immunological tool when interpreted in the light of other clinical and noninvasive cardiac diagnostic tests. An enlarging cardiac silhouette, perihilar edema, and pleural effusion on chest roentgenography each suggest graft rejection and/or fluid overload. Of course, isolated pulmonary infiltration may be confirmational evidence of infection. New arrhythmias and/or persistently diminishing combined QRS voltage on electrocardiography are considered evidence of graft rejection until proven otherwise. A gradual or dramatic fall in percentage of shortening fraction and/or increasing thickness of the posterior left ventricular wall on repeated M-mode echocardiography are also suggestive of rejection. An individual recipient profile, developed over the first 6–8 post-transplant weeks, provides a norm against which later changes may be compared. Clinical intuition clearly plays a significant role in the interpretation of test results.

A useful philosophy that has evolved from the experience with this series of transplanted infants suggests that "the transplanted baby ought to be a *well* baby." Any deviation from wellness during the first 6 post-transplant months renders graft rejection highly suspicious, provided that infection and/or drug toxicity can be comfortably ruled out. Experience with these recipients implies that noninvasive surveillance is adequate for this

age group. Late myocardial biopsies from the five oldest survivors showed neither rejection nor fibrosis of their cardiac grafts.

Conclusions

Assuming recipient immune response and infection are controllable (if not preventable), the "Achilles' Heel" of infant heart transplantation is donor organ availability. This issue will become more intense as competition for infant organs increases among transplant centers. If each one were utilized, there would likely be enough potential infant organ donors in North America annually to meet the demand. Therefore, obligatory steps in the evolution of infant heart transplantation are enhanced public awareness, professional education, and willing participation. Donor awareness must extend to grieving parents, reticent bedside pediatricians, nurses, social workers, and coroners' offices. It must become inappropriate to terminate artificial life-support for a brain-dead newborn or infant without first considering whether or not the infant is an acceptable organ donor. Obtaining the parents' and coroner's consent, and initiating a nationwide UNOS search by way of local procurement agencies for a compatible recipient are all that is required.

A second way to enhance infant donor organ supply is to create a mechanism within existing laws for utilizing some of the nearly 2000 liveborn anencephalics delivered annually in North America. To this end, LLUMC, in connection with other supportive institutions, has devised a protocol under which maintenance care is provided to anencephalic infants of consenting families until brain-death diagnosis consistent with current law is documented. Thus far, of 14 donors for this series of transplanted infants, only one was an anencephalic infant who met brain death criteria. The donor heart has functioned well in its recipient for 6 months.

Finally, cross-species transplantation should continue to be explored. Immediate availability, pretransplant immunologic selection, and ability to control the somewhat more intense host cellular immune response continue to make this an attractive donor option. Well-conceived and executed clinical trials of xenotransplantation are inevitable and should be accomplished.

The short-term results of cardiac transplantation in very early infancy appear excellent and compare favorably with cardiac transplantation results in any other age group. Life quality is generally superb. Chronic immunosuppression is minimal, well-tolerated without apparent side effects, and does not seem to produce increased vulnerability to lethal infectious complications. The protocol for noninvasive surveillance appears adequate. Time alone will resolve the questions concerning long-term outcome.

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DISCUSSION

DR. CONSTANTINE MAVROUDIS (Louisville, Kentucky): I congratulate the authors on a well-presented landmark paper showing the excellent short-term results of infant orthotopic transplantation for severe forms of congenital heart disease.

Dr. Bailey has pioneered this field with thoughtful and well-executed animal research and now has followed with this superb clinical study. Our experience in Louisville has mirrored his in Loma Linda.

From June 1986 to May 1988, we evaluated 18 infants for orthotopic cardiac transplantation. Sixteen infants had hypoplastic left heart syndrome, one had endocardial fibroelastosis, and one had anomalous pulmonary artery origin of the left main coronary artery. All were newborns, except for the patient with the anomalous coronary who was 11 months old.